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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,505	12/10/2001	Peter W. Laird	47675-9	8355

22504 7590 03/26/2003

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,505	LAIRD ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed 12/10/01. Currently, claims 27-69 are pending.

Priority

2. This application claims priority to containuation application 09/311,912, filed May 14, 1999.

Specification

3. The use of the trademark TaqMan, LightCycler, Sunrise has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

New Matter

4. Claims 35, 37, 46, 48, 58, 60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "a molecular beacon-type probe," and "a scorpion-type primer" are included. The amendment proposes that the new claim

language is supported on page 8, 15 and 16 of the specification. However, the specification does not describe or discuses "a molecular beacon-type probe," and "a scorpion-type primer." Instead the specification describes dual probe technology, fluorescent primers, and fluorescence based quantitative PCR. This description does not support "a molecular beacon-type probe," and "a scorpion-type primer". The concept of "a molecular beacon-type probe," and "a scorpion-type primer" does not appear to be part of the originally filed invention. Therefore, "a molecular beacon-type probe," and "a scorpion-type primer" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 27-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 27-59 are indefinite over the recitation "an amplification-mediated" because it appears that the claim is missing a word. The claim appears to be missing a noun which the adjective describes. Moreover, Claims 27-59 are indefinite over the recitation "or in a property thereof in relation to another probe or primer" because it is unclear what is encompassed by the claims. The specification fails to specifically define

what constitutes a property thereof in relation to another probe or primer. Therefore, the metes and bounds of the claimed invention are unclear.

B) Claims 34-35, 45-46, 57-58, 67 rely upon a trademark within the claims. As provided by the MPEP 2173.05(u),

If the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of the 35 U.S.C. 112, second paragraph. Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. In fact, the value of a trademark would be lost to the extent that it became descriptive of a product, rather than used as an identification of a source or origin of a product. Thus, the use of a trademark or trade name in a claim to identify or describe a material or product would not only render a claim indefinite, but would also constitute an improper use of the trademark or trade name.

Therefore, in view of the MPEP, the claims are indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 27-30, 36, 38-41, 47, are rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalgo et al (Nucleic Acids Research, Vol. 25, No. 12, pages 2529-2531, 1997).

Gonzalgo et al. (herein referred to as Gonzalgo) teaches a method for detecting cytosine methylation and methylated CpG islands within genomic sample of DNA by contacting the sample of genomic DNA with bisulfite, amplifying the converted nucleic acid with primers which distinguish between unmethyalted and methylated nucleic acids such that at least one oligonucleotide probe is a CpG specific probe and detecting the methylated nucleic acid based on an amplification mediated change or property thereof in relation to another probe or primer. Specifically Gonzalgo teaches a method of rapid quantitation of methylation differences at specific sites using methylation-sensitive single nucleotide primer extension (Ms-SnuPE). As specifically shown in Figure 1, the method includes obtaining a genomic DNA sample (limitations of Claim 27a), treating the sample with bisulfite treatment (limitations of Claim 27a, 29-30), amplifying the template to obtain PCR products (limitations of Claim 27b), electrophoresing the products and isolating from agarose gels, incubation with Ms-SnuPE primers to enable a primer extension reaction (limitations of Claim 27b), electrophoresed and visualized by exposure (limitations of Claim 27c)(col. 2530, col. 1). It is noted that primers function to probe a template nucleic acid prior to the extension assay. Therefore, the claim is read broadly to encompass using the Ms-SnuPE oligonucleotides which probe and then extend to be encompassed by the claim which requires at least one oligonucleotide probe capable of distinguishing between methylated and unmethylated nucleic acid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 61-65, 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al (Nucleic Acids Research, Vol. 25, No. 12, pages 2529-2531, 1997) in view of Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995).

Gonzalgo et al. (herein referred to as Gonzalgo) teaches a method for detecting cytosine methylation and methylated CpG islands within genomic sample of DNA by contacting the sample of genomic DNA with bisulfite, amplifying the converted nucleic acid with primers which distinguish between unmethyalted and methylated nucleic acids

such that at least one oligonucleotide probe is a CpG specific probe and detecting the methylated nucleic acid based on an amplification mediated change or property thereof in relation to another probe or primer. Specifically Gonzalgo teaches a method of rapid quantitation of methylation differences at specific sites using methylation-sensitive single nucleotide primer extension (Ms-SnuPE). As specifically shown in Figure 1, the method includes obtaining a genomic DNA sample (limitations of Claim 27a), treating the sample with bisulfite treatment (limitations of Claim 27a, 29-30), amplifying the template to obtain PCR products (limitations of Claim 27b), electrophoresing the products and isolating from agarose gels, incubation with Ms-SnuPE primers to enable a primer extension reaction (limitations of Claim 27b), electrophoresed and visualized by exposure (limitations of Claim 27c)(col. 2530, col. 1). It is noted that primers function to probe a template nucleic acid prior to the extension assay. Therefore, the claim is read broadly to encompass using the Ms-SnuPE oligonucleotides which probe and then extend to be encompassed by the claim which requires at least one oligonucleotide probe capable of distinguishing between methylated and unmethylated nucleic acid.

Gonzalgo does not specifically teach packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Gonzalgo with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and

reagents of Gonzalgo into a kit, as taught by Ahern for the express purpose of saving time and money.

9. Claims 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al (Nucleic Acids Research, Vol. 25, No. 12, pages 2529-2531, 1997) in view Whitcombe et al (US Pat. 6,270,967, August 2001).

Gonzalgo does not specifically teach using a TaqMan probe to detect allele specific differences in genomic DNA which have been treated with bisulfite to analyze methylation status of the nucleic acid.

However, Whitcombe illustrates the use of a TaqMan probe (xyz) for allele discrimination of the ASO element (Figure 10, col. 8, lines 58-62). Whitcombe teaches that the use of TaqMan probe allows realtime or end point detection of the released fluorophore.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified an improved the method of Gonzalgo for detection of allele specific detection using a TaqMan probe as suggested by Whitcombe. Whitcombe specifically teaches using a TaqMan probe in the ASO detection of an allele. Therefore, the ordinary artisan would have recognized that using a TaqMan probe as opposed to an ASO hybridization would have the expected benefits of realtime detection of the released fluorophore. Therefore, the ordinary artisan would have been motivated to use a TaqMan probe in lieu of an ASO primer extension, as taught by Herman.

10. Claims 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al (Nucleic Acids Research, Vol. 25, No. 12, pages 2529-2531, 1997) in view of Wittwer et al (US Pat. 6,140,054, October 2000).

Gonzalgo et al. (herein referred to as Gonzalgo) teaches a method for detecting cytosine methylation and methylated CpG islands within genomic sample of DNA by contacting the sample of genomic DNA with bisulfite, amplifying the converted nucleic acid with primers which distinguish between unmethyalted and methylated nucleic acids such that at least one oligonucleotide probe is a CpG specific probe and detecting the methylated nucleic acid based on an amplification mediated change or property thereof in relation to another probe or primer. Specifically Gonzalgo teaches a method of rapid quantitation of methylation differences at specific sites using methylation-sensitive single nucleotide primer extension (Ms-SnuPE). As specifically shown in Figure 1, the method includes obtaining a genomic DNA sample (limitations of Claim 27a), treating the sample with bisulfite treatment (limitations of Claim 27a, 29-30), amplifying the template to obtain PCR products (limitations of Claim 27b), electrophoresing the products and isolating from agarose gels, incubation with Ms-SnuPE primers to enable a primer extension reaction (limitations of Claim 27b), electrophoresed and visualized by exposure (limitations of Claim 27c)(col. 2530, col. 1). It is noted that primers function to probe a template nucleic acid prior to the extension assay. Therefore, the claim is read broadly to encompass using the Ms-SnuPE oligonucleotides which probe and then

extend to be encompassed by the claim which requires at least one oligonucleotide probe capable of distinguishing between methylated and unmethylated nucleic acid.

Gonzalgo does not specifically teach using a FRET probe to detect allele specific differences in genomic DNA which have been treated with bisulfite to analyze methylation status of the nucleic acid.

However, Wittwer et al. (herein referred to as Wittwer) teaches a method of using FRET probes to detect polymorphisms. Wittwer teaches that the methods of ASO hybridization require time consuming multiple manual steps. Therefore, Wittwer uses melting temperatures of fluorescent hybridization probes that hybridize to a PCR amplified region to identify polymorphisms (col. 1, lines 30-35). Wittwer teaches designing oligonucleotide probes identical in sequence to the complementary wild type sequence which will dissociate from the locus containing a mutation at a lower temperature than it will from the wild type locus (col. 4, lines 5-15). The probes of Wittwer contain fluorescent labeled dyes that when in close proximity the resonance energy transfer is high (col. 9, lines 7-10). The probes may comprise multiple sets of FRET oligonucleotide pairs which can be labeled with different fluorescent resonance energy transfer pairs (col. 12, lines 55-65). The method allows for a rapid procedure that can be conducted within a single reaction vessel for detecting polymorphisms in genomic DNA samples (col. 7, lines 15-25).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified and improved the method of Gonzalgo which detected allele specific differences in genomic DNA following bisulfite treatment

using ASO probes with the allele specific detection method of Wittwer. Wittwer specifically teaches the method of using FRET probes to detect the presence of alleles or polymorphisms is less time consuming and require less manual steps. Moreover, Wittwer's method allows detection in a single reaction vessel. Therefore, the ordinary artisan would have been motivated to have detected allele specific differences in bisulfite treated DNA using FRET probes for the specific benefits taught by Wittwer.

11. Claims 27-30, 36, 50-53, 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herman et al (US Pat. 6,017,704, January 25, 2000).

Herman et al. (herein referred to as Herman) teaches a method of detection of methylated nucleic acids using agents which modify unmethlated cytosine and distinguishing modified methylated and non-methylated nucleic acids. Herman teaches a method for detecting cytosine methylation and methylated CpG islands within genomic sample of DNA by contacting the sample of genomic DNA with bisulfite, amplifying the converted nucleic acid with primers which distinguish between unmethyalted and methylated nucleic acids such that at least one oligonucleotide probe is a CpG specific probe and detecting the methylated nucleic acid based on an amplification mediated change or property thereof in relation to another probe or primer. Specifically Herman teaches using MSP primers that are specifically designed to recognize CpG sites to take advantage of the differences in methylation to amplify specific products to be identified (col. 5, lines 3-5). Herman teaches that the "only technique that can provide more direct analysis than MSP for most CpG sites within a

defined region is genomic sequencing" (col. 5, lines 30-35). Herman teaches a method for detecting a methylated CpG containing nucleic acid by obtaining nucleic acid and treating the nucleic acid with an agent that modifies unmethylated cytosine (col. 5, lines 58-63). The agent is preferably sodium bisulfite which modifies unmethylated cytosine, but not methylated cytosine (col. 6, lines 9-13)(limitations of Claim 29-30). Moreover, amplification is carried out using primers specific for CpG-specific oligonucleotides such that the primer distinguish between modified methylated and non-methylated nucleic acids and finally detecting the methylated nucleic acids (col. 5, lines 60-67). Herman teaches that the amplified products are preferably identified as methylated or non-methylated by sequencing (col. 9, lines 51-55). Among the sequencing methods suggested by Herman, allele-specific oligonucleotide probe analysis is listed (col. 9, lines 55-65). Allele-specific oligonucleotide (ASO) probes are specific probes which allow differentiation between different sequences.

While Herman does not specifically teach a method involving ASO probes. ASO probe detection is among the list of means for sequencing the amplified products to identify methylated or non-methylated sequences. Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified and improved the method of Herman by using ASO probes for detecting the amplified products. Herman specifically teaches that the only technique that can provide a more direct analysis than MSP is genomic sequencing. Therefore, the ordinary artisan would have been motivated to have combined the MSP method of Herman with the genomic sequencing methods of Herman to obtain a modified and

improved method of detecting methylated or non-methylated products. Allele specific oligonucleotide probes are used to distinguish alleles from one another. Since the genomic nucleic acid has been treated to convert un-methylated nucleic acids, the sequence differs between the methylated and unmethyalted nucleic acids. The ordinary artisan would recognize that based upon the teachings of Herman that ASO probes are a means of sequencing that using this means of sequencing to provide an improved modified method would have been obvious at the time the invention was made.

12. Claims 31-34, 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herman et al (US Pat. 6,017,704, January 25, 2000) as applied to Claims 27-30, 36, 50-53, 59 above, in view of Wittwer et al (US Pat. 6,140,054, October 2000).

Herman does not specifically teach using a FRET probe to detect allele specific differences in genomic DNA which have been treated with bisulfite to analyze methylation status of the nucleic acid.

However, Wittwer et al. (herein referred to as Wittwer) teaches a method of using FRET probes to detect polymorphisms. Wittwer teaches that the methods of ASO hybridization require time consuming multiple manual steps. Therefore, Wittwer uses melting temperatures of fluorescent hybridization probes that hybridize to a PCR amplified region to identify polymorphisms (col. 1, lines 30-35). Wittwer teaches designing oligonucleotide probes identical in sequence to the complementary wild type sequence which will dissociate from the locus containing a mutation at a lower temperature than it will from the wild type locus (col. 4, lines 5-15). The probes of

Wittwer contain fluorescent labeled dyes that when in close proximity the resonance energy transfer is high (col. 9, lines 7-10). The probes may comprise multiple sets of FRET oligonucleotide pairs which can be labeled with different fluorescent resonance energy transfer pairs (col. 12, lines 55-65). The method allows for a rapid procedure that can be conducted within a single reaction vessel for detecting polymorphisms in genomic DNA samples (col. 7, lines 15-25).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified and improved the method of Herman which detected allele specific differences in genomic DNA following bisulfite treatment using ASO probes with the allele specific detection method of Wittwer. Wittwer specifically teaches the method of using FRET probes to detect the presence of alleles or polymorphisms is less time consuming and require less manual steps. Moreover, Wittwer's method allows detection in a single reaction vessel. Therefore, the ordinary artisan would have been motivated to have detected allele specific differences in bisulfite treated DNA using FRET probes for the specific benefits taught by Wittwer.

13. Claims 35, 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herman et al (US Pat. 6,017,704, January 25, 2000) as applied to Claims 27-30, 36, 50-53, 59 above, in view of Whitcombe et al (US Pat. 6,270,967, August 2001).

Herman does not specifically teach using a TaqMan probe to detect allele specific differences in genomic DNA which have been treated with bisulfite to analyze methylation status of the nucleic acid.

However, Whitcombe illustrates the use of a TaqMan probe (xyz) for allele discrimination of the ASO element (Figure 10, col. 8, lines 58-62). Whitcombe teaches that the use of TaqMan probe allows realtime or end point detection of the released fluorophore.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified an improved the method of Herman for detection of allele specific detection using a TaqMan probe as suggested by Whitcombe. Whitcombe specifically teaches using a TaqMan probe in the ASO detection of an allele. Therefore, the ordinary artisan would have recognized that using a TaqMan probe as opposed to an ASO hybridization would have the expected benefits of realtime detection of the released fluorophore. Therefore, the ordinary artisan would have been motivated to use a TaqMan probe in lieu of an ASO hybridization, as taught by Herman.

14. Claims 61-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herman et al (US Pat. 6,017,704, January 25, 2000) as applied to Claims 27-30, 36, 50-53, 59 above, in view of Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995).

Herman does not specifically teach packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Herman with

the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Herman into a kit, as taught by Ahern for the express purpose of saving time and money.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 27-32, 38-43, 50-55, 61-67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-26 of U.S. Patent No. 6,331,393 (December 18, 2001).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claim 27-32, 38-43, 50-55, 61-67 of the instant application is generic to all that is recited in Claim 1-26 of U.S. Patent No. 6,331,393. That is, Claim 1-26 of 6,331,393 falls entirely within the scope of Claim 27-32, 38-43, 50-55, 61-67, or in other words, Claim 27-32, 38-43, 50-55, 61-67 is anticipated by Claim 1-26 of 6,331,393. Here, claim 27 recites a method for detecting cytosine methyaltion and methylated CpG islands by contacting a genomic sample of DNA with a modifying agent, amplifying the nucleic acid with primers and detecting the methylated nucleic acid based on an amplification- medicated, or amplification product-mediated change in a property of the CpG-specific probe or in a property thereof in relation to another probe or primer. The claims of U.S. Patent No. 6,331,393 are directed specifically to detecting the methylated nucleic acid based on amplification-mediated displacement of the Cp-G specific probe. Therefore, the specific detection means claimed falls within the scope of the broad genus of detection methods allowed in Claim 27, 38, 50. Moreover, the Claims drawn to the kits, namely Claim 61 of the instant application and Claim 20 of 6,331,393 differ only in the recitation of the probe which is based on amplification-mediated displacement. Therefore, the claims are not patentable distinct from one another.

Conclusion

16. No claims allowable.

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Xiong et al. (Nucleic acids Research, Vol. 25, No. 12, pages 2532-2534, 1997). Xiong teaches a quantitative technique called COBRA which introduces methylation dependant sequence differences into genomic DNA using sodium bisulfite treatment and then PCR amplified (limitations of Claim 28, 29, 30). The PCR products are digested, electrophoresed, electroblotted, oligo hybridized and phosphoimager quantified (page 2532, col. 2). As specifically seen in Figure 1, genomic DNA was treated with sodium bisulfite (limitations of Claim 27a). PCR reactions were performed using primers complementary to the converted DNA sequences with no CpG dinucleotides in the corresponding region of the original unconverted DNA (limitations of Claim 27b). The PCR products are cleaved and separated on a gel, transferred by electroblotting to a membrane. The membranes are then hybridized with a 5'-end-labeled oligonucleotide (limitations of Claim 27c). The probe which is 5'end labeled distinguishes between unmethylated and methylated nucleic acid, as seen in Figure 1. The probe of Xiong is not a CpG-specific probe. Therefore, Xiong does not teach every limitation of the claimed invention.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
March 13, 2003

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600